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FORM PTO-1390 (REV. 1-98) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
425-736P	
U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	
09/380310	

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/JP98/01360	March 26, 1998	March 28, 1997

TITLE OF INVENTION
ORAL MEDICINE PREVENTING UNPLEASANT TASTE AND THE LIKE

APPLICANT(S) FOR DO/EO/US
UKAI, Koji; HARADA, Tsutomu; SUZUKI, Yasuyuki

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39 (1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(3)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(2)).
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98./-1449 and International Search Report (PCT/ISA/210)

12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☐ A substitute specification.

15. ☐ A change of power of attorney and/or address letter.

16. ☒ Other items or information:
    1.) Zero (0) sheets of Formal Drawings

Rec'd PCT/PTO 31 AUG 1999

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
NEW 09/380310	PCT/JP98/01360	425-736P

17. ☒ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO. **$970.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$840.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO. **$760.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$670.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4). **$96.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 840.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total Claims	8 - 20 =	0	X $18.00	$ 0	
Independent Claims	2 - 3 =	0	X $78.00	$ 0	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)	No		+ $260.00	$ 0	
TOTAL OF ABOVE CALCULATIONS =				$ 840.00	
Reduction of ½ for filing by small entity, if applicable. Verified Small Entity statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).				$	
SUBTOTAL =				$ 840.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐20 ☐30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$	
TOTAL NATIONAL FEE =				$ 840.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$ 40.00	
TOTAL FEES ENCLOSED =				$ 880.00	
				Amount to be: refunded	$
				charged	$

a. ☒ A check in the amount of $ **880.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account. No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2448.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

Send all correspondence to:
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SIGNATURE

STEWART, RAYMOND C.
NAME

21,066
REGISTRATION NUMBER

/dll August 31, 1999

PATENT
425-736P

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant:	UKAI, Koji et al		
Int'l. Appl. No.:	PCT/JP98/01360		
Appl. No.:	New	Group:	
Filed:	August 31, 1999	Examiner:	
For:	ORAL MEDICINE PREVENTING UNPLEASANT TASTE AND THE LIKE		

PRELIMINARY AMENDMENT

BOX PATENT APPLICATION
Assistant Commissioner for Patents
Washington, DC 20231

August 31, 1999

Sir:

The following Preliminary Amendments and Remarks are respectfully submitted in connection with the above-identified application.

AMENDMENTS

IN THE SPECIFICATION:

Please amend the specification as follows:

Before line 1, insert --This application is the national phase under 35 U.S.C. § 371 of PCT International Application No. PCT/JP98/01360 which has an International filing date of March 26, 1998, which designated the United States of America.--

REMARKS

The specification has been amended to provide a cross-reference to the previously filed International Application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By #32,868
for Raymond C. Stewart, #21,066

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RCS/dll
425-736P

(Rev. 03/30/99)

Description

Oral medicine preventing unpleasant taste and the like

Field of the Invention

The present invention relates to an oral administration composition or an oral medicine which can prevent an unpleasant taste.

Prior Art

For masking a medicine having an unpleasant taste, a lot of techniques have been developed. For example, there is known a method for coating a granulated agent with a water-soluble film (JP-A 4-282312), and a method for obtaining a powder and the like by melting a waxy substance having a melting point in the range of 40 to 100°C wherein a medicine having an unpleasant taste is allowed to be dispersed and then solidified (JP-A 7-267850). On the other hand, for liquids, in order to improve the feeling of taking medicine, there is known a method to use liquids on oral administration such as syrups, which is widely used as a dosage form suitable for infants, aged people, etc. Although syrup is a dosage form with a sweet taste, when a melted medicine has an unpleasant taste, it is difficult to administer it, because a mere sweet taste cannot prevent an unpleasant taste, and in addition, compliance of a patient is lowered. Moreover, in JP-A 4-346937, as a method for reducing a bitter taste, there has been disclosed a method

for reducing a bitter taste which comprises the step of adding a gelling agent selected from agar, gelatin or κ-carrageenan, and a seasoning agent to a substance having a bitter taste, so that a jelly state for seasoning is obtained. This method reduces a contact of a bitter taste substance with a tongue by making a jelly state, and a partly melted bitter taste substance masks a bitter taste by the use a seasoning agent.

With a view to masking a medicine having an unpleasant taste, a lot of techniques have been examined as described above, but they have a complicated manufacturing process, an inadequate effect and a problem in quality. Thus, they have not yet been satisfactory, so that a further technique is required.

Disclosure of the Invention

The present invention is directed to an oral medicine composition or an oral medicine preventing an unpleasant taste, which comprises a basic medicine having the unpleasant taste and an anionic polymer, or a method for preventing the same.

A basic substance referred to in the present invention means that its free form shows basicity, and in case of the formation of a salt form, it is not necessarily basic.

In the present invention, a basic medicine having an unpleasant taste should not be limited, therefore, among

orally administrated medicines such as an antibiotic substance, an antidementia medicine, an antiplatelet medicine, an antidepressive medicine, a medicine for improving metabolism of a brain circulation, or an antiallergic medicine, any basic medicine may be used so long as it is one having an unpleasant taste such as a bitter taste, stimulation etc. Embodied examples of the basic substance include ticlopidine hydrochloride, maprotiline hydrochloride, iphenprodil tertrate, berberine hydrochloride, digitoxin, sulpyrine, azelastine hydrochloride, etilefrine hydrochloride, diltiazem hydrochloride, propranolol hydrochloride, chloramphenicol, aminophylline, erythromycin, phenobarbital, calcium pantothenic acid, indeloxazine hydrochloride, aminoguanidine hydrochloride, donepezil hydrochloride, (RS)-1-(isopropoxycarbonyloxy)ethyl(+)-(6R,7R)-7{(z)-2-(2-aminothiazole-4-yl)-2-hydroxyiminoacetamide}-3-N,N-dimethylcarbamoyloxymethyl-8-oxo-5-thia-1-azabicyclo[4.2.0]octo-2-en-2-carboxylate hydrochloride salt, cefcapene hydrochloride and the like. Among these compounds, for donepezil hydrochloride and (RS)-1-(isopropoxycarbonyloxy)ethyl(+)-(6R,7R)-7{(z)-2-(2-aminothiazole-4-yl)-2-hydroxyiminoacetamide}-3-N,N-dimethylcarbamoyloxymethyl-8-oxo-5-thia-1-azabicyclo[4.2.0]octo-2-en-2-carboxylate hydrochloride salt, an especially excellent effect is exerted. Donepezil hydrochloride is chemically named 1-benzyl-4-(5,6-

dimethoxyindanon-2-yl)methylpiperidine hydrochloride salt, which is therapeutic medicine for Alzheimer disease of a slight to a medium degree, and its aqueous solution has a sharp bitterness and a numbness in a mouth. In addition, (RS)-1-(isopropoxycarbonyloxy)ethyl(+)-(6R,7R)-7{(z)-2-(2-aminothiazole-4-yl)-2-hydroxyiminoacetamide}-3-N,N-dimethylcarbamoyloxymethyl-8-oxo-5-thia-1-azabicyclo[4.2.0]octo-2-en-2-carboxylate hydrochloride is an effective antibiotics on oral administration, however, it has a strong bitter taste.

Although an anionic polymer referred to in the present invention should not especially be limited, an acidic polysaccharide is preferable, and typical examples include carrageenan, chondroitin sulfate, dextran sulfate, alginic acid, gerun gum, xanthan gum and a salt form thereof. With regard to carrageenan, some kinds such as ι, κ, λ and the like are known, and any kind can be used, and especially, for liquids or jellies, κ-carrageenan and λ-carrageenan are preferable, and dextran sulfate is also preferable.

For solids, especially κ-carrageenan, chondroitin sodium sulfate and sodium alginate are preferable.

Carrageenan on the market can be used, and it is obtainable from FMC Corporation : USA, Systems Bio Industries Co., Ltd. etc.

An oral medicine regarding the present invention means a dosage form which can be orally administrated as

solids, liquids or jellies. Typical examples of the solids include granules, fine granules, powders, tablets, pills etc., and typical examples of the liquids include syrups, elixirs, emulsions, suspensions and the like, and especially, a case of granules, fine granules, powders, syrups and jellies are preferable.

These dosage forms are described in the Japanese Pharmacopoeia except for jellies.

A method for administration of an oral medicine related to the present invention should not be especially limited, and according to a property of a medicine, the oral medicine can be orally administrated one to several times per day before, after or between meals.

Since the amount of a medicine in solids is different according to a property of a medicine, it is not generally spoken, but the amount of the medicine at one administration is usually in the range of 0.1 to 1000 mg.

The concentration of a medicine in oral liquids which prevents an unpleasant taste is usually in the range of 0.1 to 500 mg/ml, preferably in the range of 0.5 to 100 mg/ml. When a medicine is donepezil hydrochloride, the concentration is preferably in the range of 0.5 to 5 mg/ml.

In the present invention, the proportion of an anionic polymer to a basic substance is usually in the range of 0.1 to 20 parts by weight, preferably 0.5 to 10 parts by weight with respect to 1 part by weight of a basic substance.

In the case that the oral medicine regarding the present invention is the solids, the medicine and the anionic polymer are homogeneously mixed to obtain an effect of preventing an unpleasant taste. Furthermore, the medicine and fillers and the like are mixed, and separately, an anionic polymer is dissolved in a solvent such as water, mixed with another binding agent, if necessary, and then gradually added to the medicine to be granulated, as a result, an effect of preventing an unpleasant taste is also obtainable. Depending upon a kind of a medicine, some medicines have greater effect preventing an unpleasant taste by being granulated.

A method for manufacturing an oral medicine preventing an unpleasant taste related to the present invention should not be especially limited, and the medicine can be manufactured by a method which is usually used. For example, for granules, fillers such as lactose, mannitol, starch and crystalline cellulose etc., disintegrants and the like such as carboxymethycellulose etc. are further mixed into a medicine and κ-carrageenan, with adding a solution wherein a binding agent such as hydroxypropylcellulose, the granules can be manufactured by the use of a granulator which is usually used. And in addition, a method for manufacturing an oral liquid medicine should not be especially limited. For example, a basic medicine and an anionic polymer are solved in water to manufacture the oral liquids. Furthermore, a sweetening

agent such as cane sugar, xylitol, mannitol, glucose, aspartame and saccharin, and a taste-reforming agent such as vanilla essence and apple odor can be added to it. Since the oral medicine related to the present invention prevents an unpleasant taste, characteristic of the medicine, such as a bitter taste, numbness and contraction, it is easily administrated and compliance of a patient improves. Especially, it is effective on infants and aged people. A mechanism that the oral medicine related to the present invention prevents an unpleasant taste is considered as follows. That is to say, it is considered that when a basic substance having an unpleasant taste brings about an interaction with an acidic polysaccharide to be dissolved in salvia, or through decrease of free forms in a solution, a bonding rate of the basic substance to a receptor of a tongue is decreased, and in addition, appearance of numbness is also decreased.

Experimental Example

Test 1

2 mg/ml of an aqueous donepezil hydrochloride solution was prepared. After 50 mg of κ-carrageenan, chondroitin sulfate or dextran sulfate was dissolved in 5 ml of the aqueous solution. Two examinees (which were represented by A and B in Table) hold the whole amount of the solution in their mouths, and then evaluated the degree of a bitter taste and numbness in accordance with five

grades. The results are shown in Table 1.

As is apparent from Table 1, a bitter taste of donepezil hydrochloride can be remarkably controlled by the addition of λ-carrageenan and the like.

Test 2

By the use of ticlopidine hydrochloride (20 mg/ml), maprotiline hydrochloride (5 mg/ml) and iphenprodil tartaric acid (4 mg/ml), an effect of carrageenan preventing a bitter taste and numbness was examined. A method of examination and a standard of evaluation were based on Test 1. The results are shown in Table 2.

As is apparent from Table 2, a bitter taste and numbness of each medicine can be remarkably controlled by the addition of carrageenan. Especially, a taste of ticlopidine hydrochloride is extremely bitter and stimulative, but it proves the extremely excellent effect of the present invention that the bitter taste and numbness can be remarkably controlled by addition of carrageenan.

Test 3

Sodium alginate, sodium chondroitin sulfate, κ-carrageenan, ι-carrageenan, mannitol, cornstarch, copolyvidon and the like were blended with (RS)-1-(isopropoxycarbonyloxy)ethyl(+)-(6R,7R)-7{(z)-2-(2-aminothiazole-4-yl)-2-hydroxyiminoacetamide}-3-N,N-dimethylcarbamoyloxymethyl-8-oxo-5-thia-1-azabicyclo-[4.2.0]octo-2-en-2-carboxylate hydrochloride salt (which was shown as a compound A in Table 3) in ratios shown in

Table 2, and granules were prepared in accordance with the method of Example 3. The test was carried out by three examinees holding 0.5 g of each granule for examination in their mouths, and the judgment was done by an evaluation standard of seven grades shown as follows.

+4: impossible to administrate because of a severe bitterness, +3: very bitter, +2: bitter, +1: a little bitter, 0: neither taste, -1: feeling no bitterness, -2: rather delicious

The results are shown in Table 3.

It is apparent from Table 3 that the granules combined with the anionic polymer related to the present invention remarkably controls a bitter taste.

Test 4

According to the treatment shown in Table 4, ticlopidine hydrochloride, κ-carrageenan, cornstarch, mannitol and hydroxypropylcellulose (which was represented by HPC-L in Table 4) were sufficiently mixed and water was then added, and they were granulated to obtain granules. Two examinees held 0.5 g of this granules in their mouths, and the judgment was done. The evaluation standard was based on Example 1. The result was shown in Table 4.

It is apparent from Table 4 that the present applied invention can prevent an extremely unpleasant taste of ticlopidine even in the solid state.

From the tests shown above, the remarkable effect of the present applied invention is evident.

Examples

Next, the present invention will be described in more detail in accordance with examples, but the scope of the present invention should not be limited by these examples.

Example 1

100 mg of donepezil hydrochloride, 300 mg of sodium saccharin and 14 g of povidone were dissolved in 50 g of purified water., and separately, 700 mg of κ-carrageenan was added to 50 g of purified water, and it was were heated at 80°C to be dissolved. After it was cooled down, both solutions were mixed, and 300 mg of methylparabene and 20 mg of propylparabene were dissolved in a small quantity of propyleneglycol to be added to the above mixture, so that syrups were manufactured.

Example 2

40 g of xylitol was added to 50 g of purified water, and they were heated at 80°C to be dissolved. And separately, 200 mg of donepezil hydrochloride was dissolved in 50 ml of purified water, and wherein 0.56 g of κ-carrageenan, 1.0 g of λ-carrageenan, 0.15 g of locust bean gum, 0.22 g of gerun gum, 0.15 g of xanthan gum, 0.19 g of sodium citrate, 0.19 g of calcium lactate, 0.94 g of lactose and 40 g of powdered hydrogenated maltose starch syrup were added, and in addition, the previously prepared xylitol-containing purified water was added therein, and they were stirred at 90°C. After the mixture was cooled

down to 80°C, 0.6 g of citric acid was mixed therein, to which purified water was added, so that the total weight was 200 g. It was pipetted into vessels in a portion of 10 g and then cooled down to manufacture jellies.

Example 3

15 g of (RS)-1-(isopropoxycarbonyloxy)ethyl(+)-(6R,7R)-7{(z)-2-(2-aminothiazole-4-yl)-2-hydroxyiminoacetamide}-3-N,N-dimethylcarbamoyloxymethyl-8-oxo-5-thia-1-azabicyclo[4.2.0]octo-2-en-2-carboxylate hydrochloride salt, 15 g of κ-carrageenan, 30 g of cornstarch and 40 g of mannitol were mixed by the use of the rolling granuator, and about 20 ml of water was slowly added therein and wet mass was manufactured, and then dried through a screen with 32 meshes, so that granules were manufactured.

Example 4

15 g of the drug substance medicine used in Example 3, 15 g of sodium condroitin sulfate and 70 g of mannitol were mixed by the use of the granulator, and about 20 ml of water was slowly added therein and wet mass was manufactured, and then dried through a screen with 32 meshes, so that granules were manufactured.

Example 5

15 g of the drug substance used in Example 3, 15 g of carrageenan (mixture of ι-carrageenan and κ-carrageenan), 15 g of copolyvidon and 55 g of mannitol were mixed by the use of the granulator, and about 15 ml of water was slowly added therein and wet mass was manufactured, and then dried

through a screen with 32 meshes, so that granules were manufactured.

Example 6

58 g of the drug substance used in Example 3, 58 g of κ-carrageenan, 120 g of cornstarch, 130 g of mannitol and 16 g of aerosil were mixed, whereon 8 g of sodium alginate dissolved in 392 ml of water and a slight amount of Red-102 pigment were sprayed by the use of the fluidized bed granulator, and then they were dried. Next, 2 g of strawberry essence was sprayed thereon and they were dried, wherein 8 g of aspartame was mixed, so that fine granules were manufactured.

Example 7

15 g of the drug substnace used in Example 3, 14.5 g of κ-carrageenan, 30 g of cornstarch and 40 g of mannitol were mixed, whereon 0.5 g of λ-carrageenan dissolved in 25 ml of water was sprayed by the use of the fluidized bed granulator, so that fine granules were manufactured.

Example 8

10 g of cefcapene pivoxil hydrochloride, 10 g of κ-carrageenan, 30 g of cornstarch, 48 g of mannitol and 2 g of aspartame were mixed by the use of a rolling granulator, and 20 ml of water was slowly added thereto and wet mass was manufactured, and then dried through a screen with 32 meshes, so that granules were manufactured.

Table 1 Standard of Evaluation

Bitterness	No Feeling	Dim Feeling	Slightly bitter	Bitter	Very bitter
Numbness	No Feeling	Dim Feeling	Slightly numb	Numb	Very numb
	−	±	+	++	+++

Results

Sample/Examinee	A		B	
	Bitterness	Numbness	Bitterness	Numbness
Donepezil hdyrochloride	+++	+++	+++	+++
Donepezil hydrochloride + κ-Carrageenan	+	±	+	+
Donepezil hydrochloride + Condroitin sulfate	++	++	+++	++
Donepezil hydrochloride + Dextran sulfate	+	±	+	+

Table 2

Sample/Examinee	A		B	
	Bitter-ness	Numbness	Bitter-ness	Numbness
Ticlopidine sulfate	+++	+++	+++	+++
Ticlopidine sulfate + κ-Carrageenan (1 mg/ml) + λ-Carrageenan (1 mg/ml)	±	++	±	++
Ticlopidine sulfate + κ-Carrageenan (2 mg/ml)	−	+	−	±
Maprotiline hydrochloride	++	+	+	+
Maprotiline hydrochloride + κ-Carrageenan (2 mg/ml)	−	−	−	−
Iphenprodil tartaric acid	+	−	++	−
Iphenprodil tartaric acid + κ-Carrageenan (2 mg/ml)	±	−	−	−

Table 3

Composition	Prescrip-tion(%)	Evalu-ater A	Evalu-ater B	Evalu-ater C
Compound A Mannitol	15 85	+4	+3	+4
Compound A Sodium alginate Mannitol	15 15 70	+1	0 to +2 Note 1	+1
Compound A Sodium condroitin sulfate Mannitol	15 15 70	0	0	0
Compound A κ-Carrageenan Cornstarch Mannitol	15 15 30 40	0	0	0
Compound A κ & ι-Carrageenan Copolyvidon Mannitol	15 15 15 55	-1	0 to +1 Note 1	0
Compound A κ-Carrageenan λ-Carrageenan (solvent was added) Cornstarch Mannitol	15 14.5 0.5 30 40	0	-1	0
Compound A κ-Carrageenan sodium alginate (solvent was added) Cornstarch Mannitol Aerosil Strawberry essence Red No. 102 Aspartame	14.5 14.5 2 30 32.5 4 0.5 Trace 2	-2	-2	-2

Note 1: When it was administered with water, the bitterness was felt afterward.

Table 4

			Control	Prescrip-tion 1	Prescrip-tion 2	prescrp-tion 3
Pre-scrip-tion	Ticlopidine		100	100	100	100
	K-Carra-geenan		0	100	200	300
	Mannitol		670	570	470	370
	Cornstarch		200	200	200	200
	HPC-L		30	30	30	30
	Total		1000	1000	1000	1000
Results	A	Bitter-ness	+	±	−	−
		Numbness	+++	+++	+	±
	B	Bitter-ness	+	+	−	−
		Numbness	+++	+++	±	−

mg/g of a granule

Claims

1. An oral medicine composition preventing an unpleasant taste which comprises a basic medicine having the unpleasant taste and an anionic polymer.

2. The medicine composition according to Claim 1 wherein the anionic polymer is at least one selected from the group consisting of carrageenan, chondroitin sulfate, dextran sulfate, alginic acid, gerun gum, xanthan gum and salts thereof.

3. The medicine composition according to Claim 1 wherein the basic medicine having the unpleasant taste is an antibiotic, an antidementia medicine, an antiplatelet medicine, an antidepressive medicine, a medicine for improving metabolism of a brain circulation, or an antiallergic medicine.

4. The medicine composition according to Claim 1 wherein the basic medicine having the unpleasant taste is donepezil hydrochloride.

5. The medicine composition according to Claim 1 wherein the basic medicine having the unpleasant taste is (RS)-1-(isopropoxycarbonyloxy)ethyl(+)-(6R,7R)-7{(z)-2-(2-aminothiazole-4-yl)-2-hydroxyiminoacetamide}-3-N,N-dimethylcarbamoyloxymethyl-8-oxo-5-thia-1-azabicyclo-[4.2.0]octo-2-en-2-carboxylate hydrochloride salt.

6. The medicine composition according to Claim 1 wherein the anionic polymer is contained in an amount of

0.1 to 20 parts by weight with respect to 1 part by weight of the basic substance having the unpleasant taste.

7. The composition according to Claim 1 wherein the medicine is granules, fine granules, powders, liquids, syrups or jellies.

8. A method for preventing an unpleasant taste which comprises the step of blending an anionic polymer with a basic medicine having an unpleasant taste.

Abstract

A composition of an oral medicine or an oral medicine which can prevent an unpleasant taste of the medicine is herein disclosed. It is granules, powders, syrups and the like which is prevented from an unpleasant taste, comprising a basic medicine having an unpleasant taste and an anionic polymer such as carrageenan.

BIRCH, STEWART, KOLASCH & BIRCH, LLP

PLEASE NOTE: YOU MUST COMPLETE THE FOLLOWING:

COMBINED DECLARATION AND POWER OF ATTORNEY

FOR PATENT AND DESIGN APPLICATIONS

ATTORNEY DOCKET NO. 425-736P

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated next to my name; that I verily believe that I am the original, first and sole inventor (if only one inventor is named below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Insert Title: Oral medicine preventing unpleasant taste and the like

Fill in Appropriate Information - For Use Without Specification Attached:

the specification of which is attached hereto. If not attached hereto,

the specification was filed on _____ as United States Application Number _____; and /or

the specification was filed on March 26, 1998 as PCT International Application Number PCT/JP98/01360; and was amended under PCT Article 19 on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I do not know and do not believe the same was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to this application, that the same was not in public use or on sale in the United States of America more than one year prior to this application, that the invention has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on an application filed by me or my legal representatives or assigns more than twelve months (six months for designs) prior to this application, and that no application for patent or inventor's certificate on this invention has been filed in any country foreign to the United States of America prior to this application by me or my legal representatives or assigns, except as follows.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Insert Priority Information: (if appropriate)

Prior Foreign Application(s) (Number)	(Country)	(Month/Day/Year Filed)	Priority Claimed
9-78568	Japan	Mar. 28, 1997	☒ Yes ☐ No
9-343265	Japan	Dec. 12, 1997	☒ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

Insert Provisional Application(s): (if any)

(Application Number) (Filing Date)

(Application Number) (Filing Date)

All Foreign Applications, if any, for any Patent or Inventor's Certificate Filed More Than 12 Months (6 Months for Designs) Prior To The Filing Date of This Application:

Insert Requested Information: (if appropriate)

Country	Application No.	Date of Filing (Month/Day/Year)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Insert Prior U.S. Application(s): (if any)

(Application Number) (Filing Date) (Status - patented, pending, abandoned)

(Application Number) (Filing Date) (Status - patented, pending, abandoned)

I hereby appoint the following attorneys to prosecute this application and/or an international application based on this application and to transact all business in the Patent and Trademark Office connected therewith and in connection with the resulting patent based on instructions received from the entity who first sent the application papers to the attorneys identified below, unless the inventor(s) or assignee provides said attorneys with a written notice to the contrary:

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PLEASE NOTE: YOU MUST COMPLETE THE FOLLOWING:

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full Name of First or Sole Inventor: Insert Name of Inventor; Insert Date This Document is Signed; Insert Residence; Insert Citizenship; Insert Post Office Address

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* DATE OF SIGNATURE